PATENT COOPERATION TREATY

EUROPEAN PHARMA PATENT DEPARTMENT
13 SEP 2006

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	11.09.2006
Applicant's or agent's file reference: PC32225A	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2005/001044	14.04.2005	22.04.2004

Applicant
WARNER-LAMBERT COMPANY LLC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

FILING	✓
DEBIT NOTE	
RENEWAL	
RECORDABLE	

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC32225A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2005/001044	International filing date *(day/month/year)* 14.04.2005	Priority date *(day/month/year)* 22.04.2004
International Patent Classification (IPC) or national classification and IPC INV. C07C255/54 A61K31/277		
Applicant WARNER-LAMBERT COMPANY LLC et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.06.2005	11.09.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Seufert, Gudrun Telephone No. +49 89 2399-8330

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-58 as originally filed

   Claims, Numbers

   1-10 received on 06.09.2005 with letter of 31.08.2005 .

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Reference is made to the following documents:

D21 WO 03/074473 A

V. Reasoned statement with regard to novelty, inventive step or industrial applicability

Novelty

The present application refers to compounds of the general formula (I) (claim 1), their use in the manufacture of a medicament (claims 6-7), a pharmaceutical composition and a kit comprising them (claims 8-10).

None of the available documents describes a compound with X^1 equal to a trifluoromethyl or a chloro group in position 3 of the phenyl ring. Claims 1, 6-7, and 8-10 as well as the dependent claims 2-5 appear therefore to meet the requirement of Art. 33(2) PCT.

Inventive step

Document D21, which may be considered as the most relevant prior art document, discloses compounds having a certain structural similarity with those of the present application for the same use. The main difference lies in the group connecting the cyano-substituted phenyl of formula (I) with the group X^2.

The problem to be solved by the present invention may therefore be considered as providing alternative compounds useful in the treatment of diseases related to the androgen receptor.

The problem has been solved by compounds according to claim 1, see examples 32-34 of the application.

None of the documents gives an indication to the skilled person that would motivate

him to modify the known prior art compounds in such a way as to arrive at the compounds of claim 3-6 of the present invention. Additionally, it was not obvious that these modified compounds would retain the desired activity.
Thus, the subject-matter of claims 1-10 may be considered as involving an inventive step.

Industrial applicability

There are no objections against the industrial applicability of the subject-matter of claim 1-10.

Further remarks:

1) The claims are not considered to meet the requirement of clarity and/or support (Art. 6 PCT) for the following reasons:

The definition iv. for the variable A in claim 1 is inconsistent with the definitions ix. - xiii. It should be noted that the definition "optionally substituted" encompasses absolutely every substituent, for example also the groups SR^1, OR^2, etc.

The term "optionally substituted" encompasses absolutely every substituent. Such a broad claim is not supported by the present application. Especially, the required activity has not been demonstrated over the whole breadth of the claim, which in addition raises doubts whether the technical problem has been solved over the whole breadth of the claims.

The embodiment of the invention described in example 10 does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

2. Claim 11 comprises all the features of claim 10 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

3. The vague and imprecise statement in the description on page 28, line 33 until page 29, line 2 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

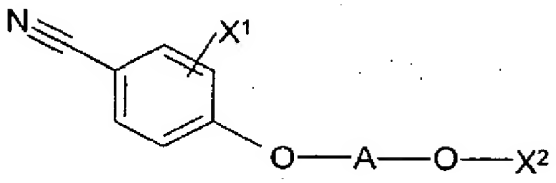
4. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D21 is not mentioned in the description, nor is this documents identified therein.

5. The description has not been adapted to the amended claims.

CLAIMS

What is claimed is:

1. A compound of the formula:



a salt or a solvate, thereof,

in which;

a) X^1 is represented by trifluoromethyl or chloro, and is located at the 3-position of the phenyl ring,

b) A is represented by a linear alkylene group containing from 2 to 10 carbon atoms, in which up to 6 hydrogen atoms may optionally be replaced by a substituent independently selected from the group consisting of:

i. halogen,
ii. cyano,
iii. hydroxy,
iv. $(C_1\text{-}C_{12})$alkyl, optionally substituted,
v. $(C_2\text{-}C_{12})$alkenyl, optionally substituted,
vi. $(C_2\text{-}C_{12})$alkynyl, optionally substituted,
vii. $(C_3\text{-}C_{10})$cycloalkyl, optionally substituted,
viii. $(C_3\text{-}C_{10})$ cycloalkyl$(C_1\text{-}C_6)$alkyl, in which the alkyl and cycloalkyl moieties may each be optionally substituted,
ix. $(CH_2)_n\text{-}SR^1$,
x. $(CH_2)_n\text{-}O\text{–}R^1$,
xi. $(CH_2)_n\text{-}NR^1R^2$,
xii. $(CH_2)_n\text{-}COOR^3$ and,

xiii. $(CH_2)_n$-$CONR^4$;

c) X^2 is represented by $(C_6$-$C_{10})$aryl, optionally substituted;

d) n, at each occurrence, is independently represented by an integer from 0 to 6;

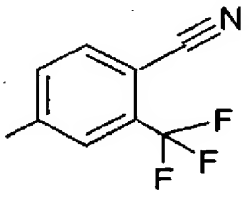
e) R^1 and R^2 are each independently represented by a substituent selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl, optionally substituted;

f) R^3 is represented by a substituent selected from the group consisting of hydrogen, and $(C_1$-$C_6)$alky, optionally substituted; and;

g) R^4 is represented by a substituent selected from the group consisting of hydrogen, and $(C_1$-$C_6)$alkyl, optionally substituted.

2. A compound according to claim 1 in which A is represented by ethylene, propylene, butylenes, or pentylene, any of which may be optionally substituted.

3 A compound according to claim 1 or 2 in which X^2 is represented by:



4. A compound according to claim 1, 2, or 3 in which A is ethylene or propylene and is substituted with at least one substituent represented by $(CH_2)_n$-O–R^1 or $(C_1$-$C_6)$alkyl.

5. A compound according to claim 1 selected from the group consisting of:

a. 4,4'-[(2S,3S)-butane-2,3-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile]);

b. 4,4'-[(2R,3R)-butane-2,3-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

c. 4,4'-[but-1-ene-3,4-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

d. 4,4'-[pentane-1,2-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

e. 4,4'-[(3-methoxypropane-1,2-diyl)bis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

f. 4,4'-[(3-ethoxypropane-1,2-diyl)bis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

g. 4,4'-[[3-(isopropylamino)propane-1,2-diyl]bis[2-(trifluoromethyl)benzonitrile];

h. 4,4'-[(6-methylhexane-1,2-diyl)bis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

i. 4,4'-[octane-1,2-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

j. 4-[1-(4-Cyano-3-trifluoromethyl-phenoxymethyl)-2,2-dimethyl-cyclopropoxy]-2-trifluoromethyl-benzonitrile;

k. 4,4'-[Propane-1,3-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

l. 4,4'-[(2-methylpropane-1,3-diyl)bis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

m. 4,4'-[butane-1,3-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

n. 4-({(3R)-3-[4-cyano-3-(trifluoromethyl)phenoxy]butyl}oxy)-2-(trifluoromethyl)benzonitrile;

o. 4-({(3S)-3-[4-cyano-3-(trifluoromethyl)phenoxy]butyl}oxy)-2-(trifluoromethyl)benzonitrile;

p. 4-{3-[4-cyano-3-(trifluoromethyl)phenoxy]-1,2-dimethylpropoxy}-2-(trifluoromethyl)benzonitrile;

q. 4,4'-[hex-1-ene-4,6-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

r. 4,4'-[(3-methylbutane-1,3-diyl)bis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

s. 4-{[3-(4-cyanophenoxy)-2-ethylhexyl]oxy}bis[2-(trifluoromethyl)benzonitrile];

t. 4,4'-[(2S,4S)-pentane-2,4-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

u. 4,4'-[heptane-1,4-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

v. 4,4'-[hexane-2,5-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

w. 4,4'-[(2S,5S)-hexane-2,5-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

x. 4-({5-[4-cyano-2-(trifluoromethyl)phenoxy]pentyl}oxy)-2(trifluoromethyl)benzonitrile;

y. 4,4'-[hexane-1,5-diylbis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

z. 4,4'-[(3-methylpentane-1,5-diyl)bis(oxy)]bis[2-(trifluoromethyl)benzonitrile];

aa. 4-(1-methoxymethyl-2-phenoxy-ethoxy)-2-trifluoromethyl-benzonitrile;

bb. 4-(1-hydroxymethyl-2-phenoxy-ethoxy)-2-trifluoromethyl-benzonitrile;

cc. (1R)-4-(1-hydroxymethyl-2-phenoxy-ethoxy)-2-trifluoromethyl-benzonitrile;

dd. (1R)-4-(1-methoxymethyl-2-phenoxy-ethoxy)-2-trifluoromethyl-benzonitrile;

ee. (1S)-4-(1-methoxymethyl-2-phenoxy-ethoxy)-2-trifluoromethyl-benzonitrile;

ff. 2-chloro-4-(2-methoxy-1-phenoxymethyl-ethoxy)-benzonitrile;

gg. 2-chloro-4-(1-phenoxymethyl-butoxy)-benzonitrile;

hh. 2-chloro-4-(1-phenoxymethyl-propoxy)-benzonitrile;

ii. 2-chloro-4-(1-phenoxymethyl-butoxy)-benzonitrile;

jj. 2-chloro-4-[1-(4-methoxy-phenoxymethyl-propoxy)-benzonitrile;

kk. 2-chloro-4-[1-(2-methoxy-phenoxymethyl-propoxy)-benzonitrile;

ll. 2-chloro-4-[1-methyl-phenoxy-ethoxy)-benzonitrile;

mm. 4-[4-(4-cyano-3-trifluoromethyl-phenoxy)- 2-hydroxy-butyloxy]-2-trifluoromethyl-benzonitrile;

nn. 4-[3-(4-cyano-3-trifluoromethyl-phenoxy)- 2-cyclohexyl-propyloxy]-2-trifluoromethyl-benzonitrile;

oo. 4-[3-(4-cyano-3-trifluoromethyl-phenoxy)- 2-cyclohexyl-propyloxy]-2-trifluoromethyl-benzonitrile;

pp. 4-[3-(4-cyano-3-trifluoromethyl-phenoxy)- 2-chloro-propyloxy]-2-trifluoromethyl-benzonitrile;

qq. 4-[8-(4-cyano-3-trifluoromethyl-phenoxy)- 2-chloro-4-hydroxy-octyloxy]-2-trifluoromethyl-benzonitrile;

rr. 4-[10-(4-cyano-3-trifluoromethyl-phenoxy)- 2-methylcyclopentyl-octyloxy]-2-trifluoromethyl-benzonitrile;

ss. 4-[10-(4-cyano-3-trifluoromethyl-phenoxy)- decyloxy]-2-trifluoromethyl-benzonitrile;

tt. 4-[7-(4-cyano-3-trifluoromethyl-phenoxy)-2-cyano-4-methyl-6-hydroxy-heptyloxy]-2-trifluoromethyl-benzonitrile;

uu. 4-(3-(3-hydroxy-4-fluoro-phenoxy)-propoxy)-2-trifluoromethyl-benzonitrile;

vv. 4-(2-cyano-4-dimethylamino-8-phenoxy-octyloxy)-2-trifluoromethyl-benzonitrile;

ww. 4-(2-dimethylamino-2-(4-cyano-phenoxy)-ethyloxy)-2-trifluoromethyl-benzonitrile;

xx. 4-(1-cyclopentyloxymethyl-3-(4-hydroxy-phenoxy)-propoxy)-2-trifluoromethyl-benzonitrile; and

yy. 4-(2-methyl-4-dimethylamino-8-phenoxy-octyloxy)-2-trifluoromethyl-benzonitrile.

6. Use of a compound according to any one of claims 1-5 in the manufacture of a medicament for inhibiting activation of the androgen receptor.

7. Use of a compound according to any one of claims 1-5 in the manufacture of a medicament for alleviating a condition selected from the group consisting of hormone dependent cancers, benign hyperplasia of the prostate, acne, hirsutism, excess sebum, alopecia, premenstrual syndrome, lung cancer, precocious puberty, osteoporosis, hypogonadism, age-related decrease in muscle mass, and anemia.

8. A pharmaceutical composition comprising a compound according to any one of claims 1-5 in admixture with one or more pharmaceutically acceptable excipients.

9. A topical pharmaceutical formulation comprising a compound according to any one of claims 1-5 in admixture with or more pharmaceutically acceptable excipients suitable for dermal application.

10. An article of manufacture comprising a compound according to any one of claims 1-5 packaged for retail distribution, which advises a consumer how to utilize the compound to alleviate a condition selected from the group consisting of acne, alopecia, and oily skin.